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THE RELATIONSHIP BETWEEN GASTRIC MUCOSAL ACIDOSIS AND THE DEVELOPMENT OF SEPSIS AND ORGAN FAILURE IN THE CRITICALLY ILL

BY

JON DAVID JUST

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science.

IN

EXPERIMENTAL SURGERY

DEPARTMENT OF SURGERY

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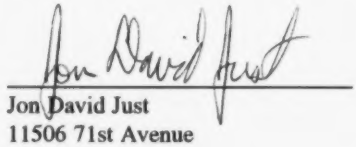

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled THE RELATIONSHIP BETWEEN GASTRIC MUCOSAL ACIDOSIS AND THE DEVELOPMENT OF SEPSIS AND ORGAN FAILURE IN THE CRITICALLY ILL submitted by JON JUST in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE in EXPERIMENTAL SURGERY.

Dr. S. M. Hamilton (Supervisor)

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June 7, 1994

ABSTRACT

The relationship between gastric mucosal acidosis and the development of sepsis and organ failure in the critically ill. Just J, Willerth M, Suarez-Almazor M, Hamilton SM, Barnett R.

Objective: To assess the relationship between the duration of gastric mucosal acidosis and the development of sepsis and multiple organ failure (MOF). Length of ICU stay, hospital stay, and hospital mortality were also recorded.

Design: Prospective comparison of outcome.

Setting: General adult ICU in a teaching hospital.

Patients: 48 consecutive critically ill patients with a predicted ICU stay $\geq$48 hours and no contraindication to gastric intubation. Patients included 31 men and 17 women, age 17 to 83 years (mean 54), with a mean APACHE II score of 19.6$\pm$7.5.

Interventions: Gastric tonometers were placed in all patients and gastric intramucosal pH was measured at admission, 2 hrs, 4 hrs, 6 hrs, 12 hrs, 24 hrs, 36 hrs, and 48 hrs.

Main Outcome Measures: A value of $\leq$7.35 was used to differentiate between normal and low gastric intramucosal pH. Organ system failure (OSF) scores, septic severity scores (SSS), length of hospital and ICU stays, and mortality were assessed.

Results: 26 of the 48 patients (54%) had mucosal acidosis at some point during the first 48 hours. Patients with gastric mucosal acidosis had higher OSF scores (2.4$\pm$1.2 *vs.* 1.5$\pm$0.7; $p<0.05$), SSS (40.2$\pm$19.9 *vs.* 26.2$\pm$11.6; $p<0.05$), and longer ICU stays (10.7$\pm$16.0 *vs.* 4.8$\pm$3.8; $p<0.05$) compared to patients without acidosis. The duration of acidosis was strongly correlated with the OSF score ($R^2=0.522$; $p<0.05$) and to the SSS ($R^2=0.457$; $p<0.05$). Patients with a longer duration of gastric mucosal acidosis were also more likely to die ($p<0.05$).

Conclusions: Critically ill patients with gastric mucosal acidosis are at increased risk for the development of sepsis and organ failure and tend to have longer ICU and hospital stays. Hospital mortality is increased in those patients with a longer duration of acidosis. Gastric tonometry is useful in predicting the development of MOF in critically ill patients.

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LIST OF ABBREVIATIONS

APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Adult Respiratory Distress Syndrome
ATP	Adenosine triphosphate
CHF	Congestive Heart Failure
CO	Cardiac Output
CO_2	Carbon dioxide
COPD	Chronic Obstuctive Pulmonary Disease
CVP	Central Venous Pressure
DO_2	Total body oxygen delivery
GCS	Glasgow Coma Scale
H^+	Hydrogen ion
HCO_3	Bicarbonate
ICU	Intensive Care Unit
IL	Interleukin
ISS	Injury Severity Score
MAP	Mean Arterial Pressure
MODS	Multiple Organ Dysfunction Syndrome
MOF	Multiple Organ Failure
MPM	Mortality Prediction Model
NIDDM	Non-Insulin Dependent Diabetes Mellitus
O_2	Oxygen
OSF	Organ System Failure
PAWP	Pulmonary Arteriolar Wedge Pressure
pHi	Gastric mucosal pH
$PtcO_2$	Peripheral transcutaneous oxygen tension
RTS	Revised Trauma Score

LIST OF ABBREVIATIONS (CONTINUED)

S.D.	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SSRC	Special Services and Research Committee (University of Alberta Hospital)
SSS	Septic Severity Score
TCA	Tricarboxycyclic acid
TNF	Tumor Necrosis Factor
UGI	Upper Gastrointestinal
VO_2	Total body oxygen consumption

INTRODUCTION

I Introductory Comments

With the development of critical care over the past several decades, many advances have been made in the treatment and support of the critically ill. However, as improvements in critical care have led to survival of individuals who would previously have died, a new syndrome has emerged, that of Multiple Organ Failure (MOF). This was first recognized by Tilney[1] in patients after ruptured abdominal aortic aneurysm and further characterized in an editorial by Baue.[2] MOF, and its most common precursor sepsis, have now become the most common causes of death in most intensive care units (ICUs).[3] Although many controversies still exist, an understanding of the pathogenesis of this syndrome is beginning to emerge. The potential for treatment of this disorder and more importantly the possibilities for its prevention are improving as this knowledge increases.

Many feel that the MOF is caused by host mediators.[4,3,5,6] An excessive response is generated as a result of ongoing stimulation of the normal host defences. Hypovolemic shock, massive intravenous fluid therapy, chest injury, and sepsis have all been identified as significant factors in the development of MOF.[7] All of these factors cause tissue injury or are associated with shock. Shock can be defined as inadequate oxygenation at the tissue level which impairs function and consequently results in tissue injury. The injured tissue can then act as a stimulus for ongoing stimulation of the host defences. When these mediators reach the systemic circulation they can cause intravascular inflammation and thus injure organs remote from the original site of insult and lead to failure of that organ. The gastrointestinal tract has also been felt by many to be the "motor" of MOF. The gut normally plays an important barrier function in preventing access of lumenal bacteria or their toxic products from gaining access to the circulation.[4] The splanchnic vasoconstriction in shock with resultant tissue hypoxia causes loss of the gut's normal function and as a consequence bacteria and their toxins may translocate into the circulation and act as a source for stimulation of the host's immune system with mediator release leading to MOF.

Resuscitation from shock is one of the most vital aspects in treating the critically ill. With the evolution of critical care and improvements in resuscitation, patients were able to survive severe insults that previously would have proven fatal. However, as mentioned earlier, this led to the recognition of

MOF as an entity with an increasingly important role in morbidity and mortality. This was puzzling as most of these patients had been successfully resuscitated, at least by traditional parameters such as heart rate, blood pressure, and urinary output. Other methods have since been developed to determine other parameters that may indicate continued inadequate oxygenation of some tissues. The concept of compensated shock refers to the state where traditional parameters have been normalized but there continues to be inadequate perfusion and oxygenation of some tissues.

The gastrointestinal tract appears to be one of the most important tissues to be affected in compensated shock. One of the earliest responses to shock is splanchnic vasoconstriction mediated by the neurohormonal mechanisms instigated by the underlying insult. As a result the gut is forced to switch to anaerobic metabolism. This results in an acidosis at the mucosal level which is indicated by a drop in pH and a rise in the carbon dioxide concentration (provided the HCO_3 remains constant). By measuring the carbon dioxide concentration in the gut, one can determine the pH of the mucosa and from this infer if there is inadequate perfusion and oxygenation of the gut to maintain normal aerobic metabolism. It was based on this concept that intestinal tonometry was developed.[8] Using an intraluminal catheter in a portion of the gastrointestinal tract to measure the mucosal pH is a potential noninvasive method of determining compensated shock.[9] Correction of the acidosis should reflect full resuscitation and may prevent MOF.[10]

Critical care patients have a wide variety of problems and underlying disorders. In order to have reliable methods of prognosticating in these patients with regard to morbidity and mortality, a variety of scoring systems have been devised. The Acute Physiology and Chronic Health Evaluation (APACHE II)[11,12] is one of the most widely used scoring systems. The Mortality Prediction Model (MPM II)[13,14,15] has been developed and can be used to predict patient outcome at the time of ICU admission. Both systems have been widely validated. These systems not only allow comparison of patients with different problems, but also different ICUs from around the world.

Definitions of organ failure and sepsis are varied and have been difficult to standardize. A number of different scoring systems for MOF have been developed, but the most widely used is that of Knaus *et al.*[16] Similarly, a number of scoring systems have been developed for sepsis. Sepsis has been

more difficult to grade in a standardized fashion and none of the sepsis scoring systems have reached widespread use. However, a modification of the scoring system developed by Stevens[17] is probably the least subjective and the most reproducible.

Sepsis and MOF remain the major causes of death in the modern ICU. These patients also tend to have longer ICU and hospital stays with resultant increased burden on health care resources. The exact etiology of MOF remains to be confirmed, but it appears that host mediators of inflammation are central to the damage caused. The stimulus to inflammatory mediator overactivation involves many factors, but tissue hypoxia from shock with resulting tissue damage appears paramount. The role of the gut with loss of its' barrier function also appears to be important. Prevention of sepsis and MOF by adequate resuscitation to prevent activation of mediators should be more successful than treating these disorders once they have become established. Currently, no method of determining adequate resuscitation exists. Intestinal tonometry shows promise of being a noninvasive method of being able to determine if patients have been resuscitated and also give a direct measure of oxygenation at the tissue level. The potential use of tonometry in preventing sepsis and MOF could be of great benefit in the care of the critically ill.

II Review of the Literature

A. Shock and Oxygen Delivery

1. Definition and Classification of Shock

As understanding of the basic underlying mechanisms of shock have improved, the definition of shock has changed. Vincent defines shock as "an imbalance between oxygen demand and oxygen supply."[18] Another way of stating this is that tissue perfusion is not sufficient to maintain normal function. Using these definitions avoids limiting shock to states of decreased cardiac output or decreased oxygen delivery.

Shock can be caused by many different processes. Classifying shock helps to differentiate the various pathophysiologic mechanisms. A classification of shock is shown in table1.

2. Pathophysiology of Shock

The three main causes of shock are inadequate circulating volume, loss of autonomic control of the vasculature, and impaired cardiac function. The compensatory mechanisms to shock include discharge of the adrenergic nervous system, release of vasoactive hormones, release of counter-regulatory hormones, release of endorphins, and activation of coagulation and inflammation. The end results of these compensatory mechanisms include venular constriction to increase preload, augmentation of cardiac contractility and heart rate, selective constriction of splanchnic and systemic arterioles to maintain blood flow to the heart and brain, release of glucose and amino acids to supply substrates as well as to create an osmolar gradient to pull water out of cells to expand the interstitial space, and retention of sodium and water to maintain the extracellular space.[19,20,21] The most important of these actions is probably the venous constriction mediated by adrenergic discharge and angiotensin II. The regional redistribution of blood flow is also important and is mediated by the same mechanisms.[22] The splanchnic circulation is very important as it has a large venous reservoir and also normally receives 30% of the cardiac output. During shock there is a marked reduction in splanchnic blood flow with an increase in venous return with most of this being mediated by angiotensin II.[23] All of these mechanisms, however, result in a compromise of the perfusion of some tissues to protect more vital tissues.

3. Cellular Metabolism

As indicated earlier, the common endpoint of all of these mechanisms of shock is tissue perfusion that is inadequate to maintain normal function. Cellular activity is dependent on a constant energy supply, most of which is supplied by adenosine triphosphate (ATP). ATP is produced in the mitochondria from the biochemical degradation of glucose. Glucose conversion to pyruvate results in the production of two moles of ATP. Under normal aerobic conditions, pyruvate enters the tricarboxycylic acid (TCA) cycle where it undergoes oxidative phosphorylation with the end products of CO_2, H_2O, and 36 moles of ATP. However, under anaerobic conditions, this can not occur and the reaction is halted at the 3 carbon chain stage of glycolysis.

Even this anaerobic reaction is limited by the accumulation of pyruvate. Conversion of pyruvate to lactate allows anaerobic glycolysis to continue. This leads to accumulation of lactate and the development of the "lactic acidosis" associated with shock. With resuscitation and the return of adequate oxygen not only is aerobic oxidative phosphorylation resumed, but the liver is also able to reconvert lactate to pyruvate so that it can be reconverted to glucose or enter the TCA cycle for production of ATP.[24]

In the event of continued shock, anaerobic metabolism continues with resultant deficiency of ATP required for normal cellular function. This leads to changes in cellular function with one of the early changes being loss of the active transport mechanisms responsible for maintaining the cell's electrochemical gradient.[25] This leads to organelle dysfunction and swelling, loss of membrane integrity, leakage of lysosomes and hydrolytic enzymes and eventual cell death.[26] When enough cells in a tissue sustain injury, tissue function becomes impaired, and an inflammatory process can be triggered. Inflammatory mediators may interfere further with oxygen and substrate delivery and thus lead to disruption of organ function.[27]

4. Oxygen Delivery

Total body oxygen delivery (DO_2) is the total amount of oxygen delivered to the body by the cardiovascular system and is dependent on the cardiac output and the arterial oxygen content. However,

by the nature of its determination, DO_2 does not necessarily reflect the amount of oxygen delivered directly to the tissues and available for their utilization. This has led to controversy as to what values of DO_2 are required by the tissues, how much of the DO_2 is actually available to the tissues, and difficulties in determining the relationship between DO_2 and total body oxygen consumption (VO_2).[28,29]

Shoemaker has studied DO_2 extensively in the critically ill population and found that survivors had a significantly higher DO_2 described as "supranormal".[30,31,32] These findings were used by Shoemaker and others to intervene to increase DO_2 in an attempt to improve patient outcome.[31,33] Only two prospective controlled trials have been done. One showed that using a protocol that aimed for supranormal cardiac index and DO_2 did have an improvement in morbidity and mortality.[34] The other did not show an improved outcome in the protocol group, but did show improved outcome in both the protocol and control groups for those patients who did reach supranormal values of DO_2.[35] These findings have led to suggestions that the goals of resuscitation from shock in critically ill patients be to "supranormal" values of DO_2.[36]

The limitations of DO_2 as an indicator of the actual tissue oxygen delivery have become apparent from the above and other studies. Barone questions the value of "supranormal" resuscitation and points out the limitations of such an approach, the potential for complications, and the need for further studies before adopting such an approach.[37] What is needed is a better indicator of oxygenation at the tissue level. Several alternative approaches have been developed and will be discussed later.[38,39,40]

Other important aspects in oxygen delivery at the tissue level are the distribution of blood flow within the tissue and the relative effects of hypoxemia and hypoperfusion. Blood flow through individual tissues is controlled through neural mechanisms, systemic neurohormonal mediators, and local mediators. The splanchnic circulation is particularly complex in this regard.[23] Thus, even knowing the oxygen delivery to a specific tissue does not give an accurate indication of blood flow at a microcirculatory level.

Decreased oxygen delivery at the tissue level can be either on a basis of decreased perfusion, hypoxia, or both. Several studies have shown that hypoxia is much better tolerated than hypoperfusion is.[41,42] This follows what appears to be logical clinically. It also has potentially important implications

for treatment, with goals of improving perfusion, particularly at a tissue level, being more important than improving oxygen content.

5. Oxygen Consumption

Oxygen consumption (VO_2) is dependent on the cardiac output and the difference between the arterial and mixed venous oxygen content. As such, it determines the oxygen utilized by the whole body and does not allow any differentiation between areas of utilization.

Normal tissues, if homogeneously perfused, can extract oxygen very efficiently and thus until DO_2 reaches very low levels, VO_2 is independent of DO_2.[27] In certain situations, however, it appears that VO_2 may become limited at higher levels of DO_2 and this has been termed pathologic supply dependency.[43] Wolf *et al* found this pathologic supply dependency of VO_2 in septic patients but not in nonseptic patients.[44] They concluded that the septic state has both impaired myocardial performance and defective peripheral oxygen extraction. In a study comparing multiple trauma patients with patients with isolated head injuries, supply dependency was found in both groups, suggesting that neurohumoral factors rather than local tissue phenomena were responsible.[45] Kaufman *et al* also showed in hypovolemic and septic shock that increasing DO_2 by fluid resuscitation increased VO_2.[46] They also concluded that since the changes were similar in both hypovolemic and septic shock that this was consistent with findings that mitochondrial utilization of oxygen is unaltered in septic shock.

In a review of oxygen utilization in sepsis, it is suggested that critically ill patients have an impaired ability to utilize oxygen in peripheral tissues even when they have higher oxygen requirements.[47] Proposed mechanisms include: peripheral arterial-venous shunting bypassing tissue capillary beds; microthrombosis and disturbed autoregulation in the microvasculature causing physiological shunting; histotoxic cellular damage resulting in uncoupling of oxidative phosphorylation and disrupting oxygen utilization; diffusion barrier from edema caused by diffuse capillary leak associated with sepsis.

Controversies still exist in consideration of DO_2, VO_2, and "supply dependency". A prospective study in critically ill patients showed spontaneous changes in DO_2 and VO_2 even when there

were no experimental interventions.[48] The authors suggest that this limits the usefulness of other studies showing supply dependency and that changes in DO_2 can likely be explained by changes in oxygen demand. This was also seen in another study where the goal was to increase DO_2 to improve survival.[28] They were able to increase the DO_2 in survivors and nonsurvivors but without a significant increase in VO_2. Vermeij *et al* compared calculated VO_2 with directly measured VO_2 and found that calculated VO_2 was not always correlated with DO_2.[49] They concluded that mathematical coupling of DO_2 and VO_2 when using calculated VO_2 may lead to erroneous conclusions about the relationship betweeen the two in post-operative and septic patients.

A recognized limitation of using global oxygen measurements is that oxygen delivery and utilization at a tissue level can not be evaluated. Even analysis of venous effluent from a tissue bed or region provides little information as it is a flow weighted average of all the different capillary beds and is therefore not a good indicator of what goes on at the cellular level.[27] Several investigators have noted this limitation in their interventional studies to improve outcome.[28,50,51] Others have looked at utilizing alternative methods of measuring perfusion at a tissue basis using subcutaneous tissue pO_2, transcutaneous pO_2, laser-Doppler skin erythrocyte flux, fingertip temperature, and intestinal tonometry.[52] Fiddian-Green suggests that intestinal tonometry is the most useful as it provides an absolute metabolic measure of the ability of the tissues to extract and utilize oxygen that meet the functional needs of the tissue at the time.[29] A prospective noninterventional study showed that mucosal pHi correlated with patient outcome whereas DO_2 and VO_2 did not.[53] An alternative form of supplying oxygen to the tissues suggested by Haglund was direct intraluminal oxygenation of the gut.[54] Although an interesting concept, this appears very impractical for clinical utility.

A final consideration in oxygen utilization in shock is the role of carbon dioxide. Johnson and Weil propose that ischemia during shock causes tissue injury not only through ischemia but also through CO_2 excess.[55] They found that venoarterial pCO_2 gradient on a systemic level correlated with perfusion failure and that comparing the gradient at an individual tissue level correlated with organ dysfunction. They suggest that venous hypercarbia may be clinically useful as a predictor because of its rapid change with changes in perfusion.

B. Resuscitation and Monitoring

As stated earlier, shock is a state of tissue perfusion insufficient to maintain normal function. It therefore appears logical that an appropriate goal for resuscitation from shock should be to restore tissue perfusion to the point of normal tissue function. Unfortunately, resuscitation is often not easy to obtain and maintain in the critically ill.

The first step in resuscitation requires an accurate diagnosis of the underlying mechanism of shock. In the previous section, the three basic mechanisms of inadequate circulating blood volume, loss of autonomic control of the vasculature, and impaired cardiac function were outlined. Differentiation between these mechanisms can often be made on clinical grounds based on history and physical examination. In critically ill patients, this differentiation may be more difficult and require further investigation and invasive monitoring.

Classically, the patient in shock has overt signs of hypotension, tachycardia, peripheral vasoconstriction, and decreased or absent urine output. Traditional goals for resuscitation have been the normalization of these values using volume replacement, cardiac augmentation using pharmacologic or mechanical means, and vasoconstricting agents as determined by the underlying mechanism. Recently, several researchers have questioned the adequacy of these traditional goals for resuscitation.[29,36,56]

With improved ICU care, patients were resuscitated from shock with a decrease in mortality from the acute event of hypotension. However, many of these patients would later go on to develop and die from sepsis or MOF.[18] Shippy found that actual blood volume as determined by indicator dilution technique was not well correlated with mean arterial pressure (MAP), central venous pressure (CVP), pulmonary arterial wedge pressure (PAWP), hematocrit, or cardiac output (CO).[57] He suggests that these commonly measured hemodynamic variables do not adequately reflect the blood volume status in critically ill patients and that many patients thought to be fully resuscitated are still hypovolemic and at risk for developing the sequelae of shock.

Shoemaker noted that survivors and nonsurvivors differed in their hemodynamic responses to shock and suggested that the "normal" hemodynamic variables determined in unstressed patients were not necessarily appropriate therapeutic goals for the person in shock.[32] He further characterized the different

hemodynamic patterns in surviving patients and determined that these patients were able to develop supranormal CO and DO_2.[30,31] Using these parameters as goals for the resuscitation of shock, Shoemaker was able to reduce mortality in critically ill postoperative patients and in high risk surgical patients.[33,34] However, another prospective randomized controlled trial using supranormal goals for resuscitation showed no difference between the protocol and control groups in mortality, development of MOF, ICU stay, or hospital stay.[35] Patients who were able to develop supranormal DO_2 (whether in the protocol or control group) did have a lower mortality and lower rate of acute respiratory distress syndrome (ARDS). This suggests that nonsurvivors may not be able to generate these supranormal hemodynamic variables and that this is the reason for their increased mortality and development of complications. In an editorial, Barone and Lowenfels question the use of maximization of DO_2 as an intervention until more evidence supporting its' value and documentation of a lack of negative effects is available.[37]

Other investigators have also shown evidence that many critically ill patients resuscitated from shock may still have inadequate tissue perfusion. Bihari found that vasodilation with prostacyclin could significantly increase DO_2 in critically ill patients.[50] However, he also demonstrated that this increased DO_2 resulted in an increase in VO_2 in nonsurvivors but not in survivors suggesting the presence of a significant oxygen debt in patients who subsequently die. This unrecognized inadequate tissue oxygenation may be an important mechanism contributing to the development of MOF and death.

Fiddian-Green suggests that "resuscitation from shock can only be complete when all evidence of supply-dependent VO_2, oxygen debt, and tissue acidosis has been eliminated."[29] He also states that the gut is selectively impaired and that it is one of the last organs to return to normality during resuscitation. In a recent review of resuscitation of shock, the concept of compensated shock is further delineated in which hypotension and oliguria are corrected, but inadequate perfusion of the splanchnic organs persists.[36] Various suggestions for better resuscitation include supranormal DO_2, measurements of subcutaneous tissue pO_2, transcutaneous pO_2, and intestinal tonometry. Subcutaneous pO_2 is felt to be more sensitive than global DO_2 but requires implantation of a subcutaneous probe. They reviewed the limitations of arterial pH and lactate as they are felt to be late indicators of inadequate perfusion.

C. Intestinal Tonometry

1. Scientific Principles

As noted earlier, traditional clinical indicators used in resuscitation may not be adequate. Using the global determinants of DO_2 and VO_2, regional perfusion is not assessed. Ideally, one should be able to assess the adequacy of tissue perfusion to assure normal aerobic function (evidence of complete resuscitation). This should preferably be done non-invasively.

Measurement of tissue oxygen tension is one method of measuring local perfusion but a practical non-invasive method of determining oxygen tension in most tissues has not yet been developed.[39] Tissue acidosis develops during inadequate perfusion and anaerobic metabolism.[42] Measurement of tissue pH using micro-probes is thus an alternative method of assessing tissue perfusion and function. Again, direct measurement of pH is not clinically useful as it is invasive and the probes required are very prone to migration.[58] Carbon dioxide levels closely correlate with tissue acidosis and CO_2 rapidly diffuses through the tissues.[59] This allows using measurement of tissue CO_2 levels as a method of determining tissue perfusion.

The concept of tonometry was first evaluated by Bergofsky in 1963.[60] Using the gallbladder and urinary bladder in dogs, he showed that the CO_2 content of saline within the lumen of the organ correlated well with CO_2 of the mucosa measured by implanted electrodes. The CO_2 content of the saline was also better correlated to the mucosal CO_2 than venous effluent CO_2.

From these basic concepts, hollow organ tonometry was developed. A tonometer consists of a catheter with a gas permeable silicone balloon at its tip. After the catheter is placed within the lumen of the gut, saline is placed within the balloon and over time, CO_2 will diffuse from the tissue into the saline down a concentration gradient until a state of equilibrium exists. The saline can then be analyzed using a standard blood gas analyzer to determine the CO_2 content.[61] The mucosal pH (pHi) can then be calculated using the Henderson-Hasselbach equation:

$$pHi = pKa + \log \frac{HCO_3(\text{arterial})}{[F] \times [CO_2(\text{saline})]}$$

where F is a time-dependent factor for partly equillibrated samples provided by the manufacturer of the device.

Two assumptions are made in this calculation. The first is that CO_2 is released in equimolar amounts with hydrogen ions generated by anaerobic metabolism and that this CO_2 freely diffuses across the gastric mucosa.[59] The second is that arterial HCO_3 is equal to gastric mucosal HCO_3.

Arterial HCO_3 is determined from an arterial blood gas and the saline CO_2 is determined from the tonometer. As mentioned earlier, the CO_2 in the saline must equilibrate with that from the mucosa. This is complete at 90 minutes but can be determined at an earlier time using correction factors. These are provided with the commercial tonometers (TRIPS-NGS catheter, Tonometrics Inc., Worchester, MA, USA).[61]

2. Validation

Fiddian-Green used tonometry while studying CO_2 back-diffusion in the stomach of dogs.[8] He showed that tonometry accurately reflected the intramural pH as determined by concurrent direct measurement using micro-glass pH probes. These measurements are more closely related to the pH of the superficial layers of the stomach than to the deeper layers. The measurements were validated over a wide range of conditions, including intestinal ischemia and the presence of exogenous acid in the stomach. He also showed that the addition of HCl affected the lumenal pH (as expected) but had no effect on the lumenal pCO_2 (and thus no effect on the calculated pHi). This was confirmed in a clinical trial as well.[62] Intestinal tonometry was again validated versus direct pH probes in pigs during endotoxemia and mesenteric occlusion.[58] Although valid during decreased flow and endotoxemia, tonometry became inaccurate during very low flow or complete mesenteric occlusion. This would be expected as the assumption that tissue HCO_3 concentration is equal to arterial HCO_3 concentration would not be valid with no arterial inflow and the calculated pHi would therefore be incorrect. An additional study with a canine model had similar findings and suggested that decreased blood flow was much more important than hypoxemia in limiting intestinal oxygen consumption.[41]

Several animal studies then looked at validation of tonometry in states that would be clinically relevant. Increasing acidosis of gastric, small intestinal, and sigmoid pHi was noted with increasing hemorrhage in pigs.[9] Gastric pHi did not fully recover after retransfusion suggesting continued ischemia. Evidence of this was seen on histologic examination of the gut. Another study of hemorrhage in a porcine model compared pHi, peripheral transcutaneous oxygen tension ($PtcO_2$), heart rate, cardiac output, blood pressure, central venous pressure, PAWP, and pulmonary artery pressures.[38] They found that $PtcO_2$ and pHi were the earliest indicators of hemorrhage and that they also correlated well with total body O_2 transport. Again they found that while pHi improved with retransfusion, it did not return to pre-hemorrhage levels.

3. Limitations

The ideal monitoring device would be non-invasive, highly accurate and precise, inexpensive, and give immediate data on which to make decisions. Few, if any such devices exist.

Tonometry is relatively non-invasive but requires the placement of a gastric tube by either the nasogastric or orogastric route and as such it has the potential complications of this placement. These complications include epistaxis, sinusitis, regurgitation with aspiration, erosion of the external nares, erosion of the pharynx or esophagus, and otitis media.

Tonometry has the obvious limitation brought about by the time required for equilibration CO_2 into the saline. Rapid sampling is therefore impossible.

Although lumenal acid does not affect the saline CO_2, if HCO_3 refluxes from the duodenum, it can interact with lumenal acid resulting in the formation of CO_2 and therefore an artifactually low pHi.[8] This was confirmed in a study on healthy volunteers that also found that this could be overcome by using H_2 antagonists.[63] This prevented secretion of lumenal acid that would interact with HCO_3. One recent study suggests that this may not completely correct this problem.[64]

As the calculation of pHi is dependent on arterial HCO_3, several potential problems exist. Systemic alkalosis or the administration of bicarbonate can result in an inaccurate pHi as the calculation of pHi is dependent on arterial HCO_3.[65,66] During states of low flow or no flow, the arterial HCO_3

will not reflect the mucosal HCO_3 and again result in an inaccurate pHi.[58] Also, in low flow states, the gastric mucosa loses some of its ability to "wash out" lumenal H^+ that back diffuses into the mucosa and that this may be responsible for a portion of the decrease in pH noted.[67] A recent study suggested that this problem could be avoided just by using the saline pCO_2 rather than the pHi as it does not require a calculation using HCO_3.[68] They showed that luminal pCO_2 correlated more closely with intestinal blood flow than pHi.

4. Clinical Application

Intestinal tonometry was devised as a potential new method of monitoring the adequacy of resuscitation from shock. This was based on the problems with resuscitation raised earlier in this discussion. Tonometry offers the potential for monitoring tissue perfusion and function, especially to the gut which may have an important role in the development of MOF.[39,42] Some investigators are strong supporters of this belief and feel that tonometry should be part of the monitoring of all critically ill patients.[29,36] Others are quite skeptical and call for further evaluation of tonometry before widespread application.[69]

Tonometry was used to predict massive bleeding from stress ulceration with high utility in critically ill patients where bleeding was only seen in those patients who had a drop in pHi.[70] In a study of patients undergoing abdominal aortic operations, abnormal pHi on sigmoid tonometry was found to be the only predictive factor for development of infectious complications.[71] A similar study showed that patients who had sigmoid ischemia the day of abdominal aortic operation all went on to develop evidence of ischemic colitis.[72] They also found sigmoid pHi to be the best predictor of mortality. A study of 80 ICU patients showed that gastric mucosal acidosis correlated with the presence of sepsis and MOF at admission as well as being predictive of mortality.[73] They also found that those patients who continued to have or developed mucosal acidosis at 12 hours after ICU admission did much worse than those patients who either never had mucosal acidosis or had normalized pHi at 12 hours. A similar study in surgical ICU patients showed pHi to be predictive of short-term mortality but not of long-term outcome.[62]

The predictive value of tonometry for development of infectious complications and mortality has been linked to the hypothesis that the development of sepsis and MOF is closely related to loss of the normal function of the gut as a barrier secondary to ischemia during shock.[4,40] This has led to the proposal that interventions to prevent or improve mucosal acidosis may reduce the frequency of MOF and mortality.[10]

Haupt showed that fluid loading in septic patients who had a low pHi led to normalization of the pHi suggesting improved gastric submucosal oxygen utilization.[74] A retrospective study of septic patients showed that either dobutamine or red blood cell transfusion could be used to increase DO_2 but that only dobutamine resulted in improved pHi.[75] No patient outcomes were reported. The only interventional study performed using pHi as the therapeutic index was by Gutierrez *et al.*[76] Patients were stratified by admission pHi (normal ≥ 7.35; low < 7.35) and then randomly assigned to a protocol or control group. The protocol group patients were resuscitated to traditional "normal" values and then if pHi remained or dropped below 7.35 or dropped by $> .10$ over 1 hour, they received a bolus of 250cc of normal saline over one hour. This was repeated two additional times if necessary and if no improvement was noted, dobutamine was started at 5 μg/kg/min for 1 hour and then increased to 10 μg/kg/min. For patients in the low admission pHi group, survival was similar in the treatment and protocol groups. In patients with a normal admission pHi, the protocol patients had a significant improvement in survival. The authors suggest that perhaps the interventions were not aggressive enough for patients with a low admission pHi as their low pHi suggested a more serious perfusion debt.

5. Comparison with Other Clinical Monitoring

A study in patients undergoing coronary artery bypass grafting compared pHi with subcutaneous pO_2, $PtcO_2$, fingertip temperature, and laser-Doppler skin erythrocyte flux.[52] They found that intra-operatively, mucosal perfusion was maintained while peripheral perfusion was decreased. Post-operatively pHi dropped initially in the ICU while peripheral perfusion improved. Peripheral perfusion returned to normal more rapidly than mucosal perfusion. They concluded that measures of peripheral perfusion correlate poorly with gut perfusion.

Another study in elective cardiac surgery patients looked at pHi, DO_2, and arterial, mixed venous, hepatic venous, and femoral venous blood gases and lactate concentrations before, during, and after cardiopulmonary bypass.[77] They found significant correlation between pHi and hepatic venous pH and lactate concentration. They concluded that pHi may provide a minimally invasive method of monitoring the adequacy of splanchnic DO_2. A further study in elective cardiac surgery patients compared pHi to splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor (TNF)-α and found that cardiopulmonary bypass was associated with increased splanchnic endotoxin levels and decreased pHi.[78] They concluded that impaired gut barrier function is responsible for the endotoxemia seen during bypass but they could not definitely conclude that mucosal acidosis was causally related. Another study in patients undergoing elective cardiac operations found that gastric mucosal acidosis was the most sensitive predictor for the development of complications.[79] A study in critically ill patients found that patients with low pHi had a significantly higher mortality in spite of having similar APACHE II scores.[73]

A prospective noninterventional study in critically ill patients compared pHi with DO_2, VO_2, oxygen extraction ratio, arterial lactate concentrations, mixed venous pO_2, and mixed venous pH.[53] They found that only pHi and mixed venous pH showed any difference between survivors and nonsurvivors. All but one of the deaths were in patients with low pHi.

Pulmonary artery catheters are required for many of these more invasive measurements. In spite of widespread use, the Swan Ganz catheter has never been shown to definitely benefit patient outcome and yet they have a relatively high morbidity and mortality associated with their use.[80-83] Others feel that the risks associated with pulmonary artery catheters have been overstated.[84-87] What the exact risk is may be disputed, but pulmonary artery catheters are an invasive and expensive form of monitoring that have not been proven to be of benefit.

A prospective study of 20 ICU patients found that pHi was correlated strongly with base deficit and that perhaps this would be a simpler and less expensive method of determining the same information.[66] They comment that base deficit is a peripheral measurement and may not accurately

reflect the splanchnic circulation. They also note that there is little published work on the predictive value of base deficit.

D. Sepsis and Multiple Organ Failure

1. Definitions

Defining sepsis would appear to be a relatively straightforward task. Stedman's Medical Dictionary defines sepsis as "the presence of various pus-forming and other pathogenic organisms, or their toxins in the blood or tissues."[88] Bone suggested that a more suitable clinical definition of sepsis would be "suspicion of infection plus the systemic response to it."[89] He also proposed various definitions for various states related to sepsis. Clinical evidence of the systemic response includes factors such as tachypnea, tachycardia, pyrexia or hypothermia, altered mental status, oliguria, and other indicators of altered organ perfusion.

An editorial at that time commended Bone for attempting to clarify terminology in sepsis, but also disagreed with many of his definitions.[90] The Canadian Multiple Organ Failure Study Group stated that not all clinical sepsis is due to established infectious foci.[91] They suggested that sepsis is a normal host response for which invasive infection is the most common stimulus, but that noninfectious stimuli may also elicit a septic response. They also note that less than 50% of patients eliciting a septic response will have bacteriologic evidence of infection. Finally, they suggest that the host's response is a continuum of physiologic severity of organ dysfunction for which multiple organ failure (MOF) is the end-point. Others have also suggested that sepsis, ARDS, and MOF are varying expressions of the same underlying mechanisms.[3]

The syndrome of MOF was first recognized in the early 1970's by Tilney.[1] Factors that were felt to be causally related to the development of MOF included shock, multiple blood transfusions, invasive sepsis, cardiovascular instability, renal injury, marginal ventilatory function, hepatic dysfunction, and severe catabolism.[2] Knaus and Wagner further characterized MOF, defining it as failure of more than one organ system, and established specific definitions of failure for the major organ systems.[16] They estimated that 15% of ICU patients develop MOF. They also found that mortality increased as the number of organs failed increased and as the length of time of organ failure increased. They showed 40% mortality for a single organ failure, 60% for two organ system failure, and nearly

100% mortality for 3 or more organ system failures lasting at least 3 days. These figures have been bourn out in other studies and remain unchanged today.[7,92,93,94]

2. Pathophysiology

The pathophysiology of MOF has stimulated much discussion, but has yet to be fully delineated. Fry noted the association of MOF with infection and suggested that sepsis and MOF were the result of uncontrolled infection.[7] In a later study, Goris noted that many patients who developed MOF did not have definite evidence of infection and suggested that MOF resulted from generalized inflammation involving massive activation of inflammatory mediators by many different mechanisms.[95] A panel discussion by the Surgical Infection Society in 1985 reviewed MOF.[6] The gastrointestinal tract was described as the "motor" of MOF, with ischemia leading to loss of the normal barrier function, translocation of bacteria and endotoxin, and activation of Kupffer cells leading to ongoing stimulation of inflammation. This continual production of inflammatory mediators and their overflow into the systemic circulation could then lead to damage of remote tissues, eventually causing organ dysfunction. These views were again restated in 1988.[96]

More recently, there have been two excellent reviews of the pathophysiology of MOF.[3,97] Deitch noted several paradoxes in MOF: organs that fail frequently are not directly injured in the initial insult; there is a lag period of days to weeks between the initial insult and the development of organ failure; not all patients with sepsis syndrome/Systemic Inflammatory Response Syndrome (SIRS) and MOF have microbiological evidence of infection; no septic focus can be identified clinically or at autopsy in more than 30% of bacteremic patients dying of sepsis and MOF; identification and treatment of suppurative infections in patients with MOF may not improve survival. This is further evidence that infection is not always present in MOF and that the host defence response is more likely responsible for these manifestations.

Deitch then reviewed the possible mechanisms of this "mediator" syndrome. The macrophage hypothesis suggests an uncontrolled inflammatory response with lack of regulation and overproduction of cytokines by macrophages at a local level with "spill-over" into the systemic circulation causing remote

organ damage. The multitude of cytokines and the present incomplete knowledge of their actions and regulation complicates the understanding of their effects. Tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-2 (IL-2) are felt to be leading contenders for the cytokines mediating the septic response.

The microcirculatory hypothesis of MOF proposes that organ injury is related to ischemia or vascular endothelial injury. Several mechanisms exist, including inadequate tissue and cellular oxygen delivery, ischemia-reperfusion injury from free radical generation, and endothelial-leukocyte interactions. The microcirculatory hypothesis overlaps and interacts with the macrophage hypothesis at many levels. It is likely that both are important in the pathogenesis of MOF, and it may be that the cytokine mediated damage is at the level of the micro-circulation.

Another hypothesis that again overlaps with the others is the gut hypothesis of MOF. This hypothesis proposes that intestinally derived bacteria or endotoxin serve to initiate, perpetuate, or exacerbate the septic state. As stated earlier, loss of the normal barrier function of the gut in shock can lead to translocation of gut bacteria and endotoxin which may stimulate cytokine production by local gut macrophages and liver Kupffer cells as well as decreased clearance of these factors.

The final major hypothesis reviewed by Deitch is that of the "two-hit phenomenon". In this theory, an initial insult primes the host such that subsequent insults may provoke a much greater host response. The inflammatory stimulus therefore does not need to be overwhelming, just persistently greater than the host's ability to clear it, to promote MOF. This process could explain some cases of MOF.

3. Clinical Correlation and Potential Interventions

Shock and the resultant inadequate oxygen delivery have been considered important in the initiation and maintenance of MOF.[27,47] Covert oxygen debt is regarded as being the underlying cause in the development of MOF in patients who have been resuscitated.[28,98] Maximizing resuscitation to eliminate this oxygen debt is regarded as a possible method of decreasing the risk of developing MOF.[5,18,99] Clinical studies looking at this possibility have yielded varying results.[35,44,46,51,100]

The relationship of infection to MOF is well established as one of the more common underlying problems.[7,101] The gastrointestinal tract is an important source of the pathogens involved in these infections.[102,103] Early deaths in septic shock are often due to refractory hypotension whereas late deaths are usually due to MOF.[92] This is felt to be the result of a defect in peripheral vasculature rather than cardiac failure.[104]

During shock, the splanchnic vasculature is affected early and to a major degree, resulting in selective mesenteric ischemia.[23] This inadequate oxygenation leads to cellular dysfunction and eventual tissue dysfunction with alteration in gut epithelial permeability.[40] This may be mediated through various mechanisms such as hypoxic damage, reperfusion injury, cytokine or other mediator induced injury, or deficient utilization or supply of key nutritional substrates.[4] Mucosal acidosis is a good indicator of the adequacy of gut oxygenation, and so tonometry has been suggested as a valuable method of assessing gut perfusion to guide therapy during shock as well as in sepsis and MOF.[39,42] This may be beneficial in decreasing the incidence or severity of MOF.[10]

Mucosal acidosis was seen during decreased blood flow as well as during the infusion of endotoxin in pigs.[58] Mucosal acidosis and increases in splanchnic endotoxin are seen during cardiopulmonary bypass.[78] It may be that these are related to each other and to the development of MOF seen in some patients after bypass but this remains unproven. It has been shown that low pHi on sigmoid tonometry is predictive of development of infectious complications as well as MOF and mortality following abdominal aortic surgery.[71,72] As noted earlier, only one study has used pHi as a basis for intervention, and this study did show a decrease in mortality.[76]

E. Scoring Systems

Comparing outcomes in critically ill patients within an ICU and between different ICUs is important in evaluating patient care and determining prognosis. It also allows one to determine the effectiveness of new therapies as well as to compare different ICUs. However, patients require intensive care for a multitude of reasons and with differing levels of severity. This has made it very difficult to determine if groups of patients with different outcomes were comparable. In an attempt to overcome these problems and to standardize variables, scoring systems were developed.

One of the most widely used scoring systems is the Acute Physiology and Chronic Health Evaluation (APACHE) classification system (see appendix 1).[11] This was developed as an objective description using commonly collected data that could be used to classify groups of patients on the basis of severity of injury. This was further modified to simplify its calculation as well as to increase its reliability in APACHE II.[12] These systems are widely used and have been shown to be valid and reproducible.[105,106] However, these and all other scoring systems are useful for analysis of patient groups and populations, but care must be taken when applying them to individual patients.

One of the problems with the APACHE II system is the inability to determine a value at the time of patient admission as it is based on the worst value in a 24 hour period, not the admission value. The Mortality Prediction Model (MPM) was developed using a multiple logistic regression model to determine which variables were important in prognosis and applying a relative weight to each so that the probability of mortality could be predicted.[13] It has the advantage of being able to use admission variables and thus be prognostic at the time of ICU admission. The MPM was further refined to also provide data at 24 and 48 hours which could then take into account changes in the patient's status over time.[14] More recently, the model has been further refined as the MPM II and validated in over 19,000 patients.[15,107] However, as with most other scoring systems, the MPM is best suited to applying to patient populations and not to individual patients.

Both the MPM and APACHE systems have been developed using broad categories of critically ill patients that may result in problems when attempting to apply them to patients with specific problems. To evaluate trauma patients, the Injury Severity Score (ISS) was developed.[108] It is calculated by

summing the squares of the acute injury severity codes for the three worst areas of the body injured. It has been subsequently validated and revised.[109,110] The Trauma Score, another system for evaluating trauma patients, was developed as a simpler system that could be used for the triage of patients.[111] This has also been simplified in the Revised Trauma Score (RTS) which is based on Glasgow Coma Scale (GCS), systolic blood pressure, and respiratory rate.[112] These various scoring systems have been compared in several studies that have shown that they each have their merits.[113,114]

Sepsis and MOF have been particularly difficult to develop scoring systems for that are reproducible and yet practical to use. Elebute and Stoner developed a system for grading sepsis based on the local effects of tissue infection, pyrexia, and secondary effects of sepsis.[115] This system is somewhat cumbersome and may not be useful in comparing patients.[116,117] Another scoring system, the Septic Severity Score (SSS), appears to be somewhat more reproducible (see appendix 3).[17] Many methods for scoring MOF have been used, but the most widely used and standardized method was outlined by Knaus and Wagner (see appendix 2).[16] The similarity between the SSS and the organ failure score of Knaus again emphasizes that sepsis and MOF appear to be expressions of the same underlying process. Sarmiento *et al* suggested combining several of the scoring systems to increase their utility.[118]

Some clinical studies have been performed to compare some of the different scoring systems. MPM and APACHE II have been found to be quite comparable although the original MPM may have overestimated mortality.[119] Arregui and others compared several scoring systems in patients in septic shock.[116] They found the organ failure scoring system of Knaus to be the best, with APACHE II also being valid. The original MPM and Elebute's grading of sepsis were not predictive of mortality in this study. Another study in trauma patients found the ISS and SSS to be predictive of ARDS and MOF but found that APACHE II was not predictive.[113] Skau compared the SSS to an acute physiology score and found both to correlate with one another and with mortality.[120]

Evaluating and comparing critically ill patients is a difficult process, and no scoring system works in all situations. However, several of these scoring systems have been proven to be valid and applicable to most patients. More detailed outlines of some of these systems are found in the appendices.

III Conclusions and Study Proposal

Sepsis and MOF are the most important causes of morbidity and mortality in most present day ICUs. As such, they are not only important in determining outcome in critically ill patients, but also a major burden to the health care system in terms of resource utilization and cost. The preceding review has discussed the proposed underlying mechanisms in the development of these syndromes and the basis for considering them both as expressions of the same underlying process.

Shock is the inadequate delivery of oxygen and nutrients to the tissues to meet their metabolic needs. Even with resuscitation of patients in shock to the traditional parameters of normal hemodynamics, many of these patients are still in covert compensated shock as demonstrated by the presence of a continued deficiency in DO_2 and risk of development of MOF. The mesenteric circulation is the major vascular bed affected in compensated shock. The relationship of the gut to MOF and the role of loss of the normal barrier function with mucosal ischemia have also been reviewed. Intestinal tonometry to measure pHi looking for mucosal acidosis is a good method of determining mucosal perfusion and evidence of function at a tissue level.

Prevention of MOF is more valuable than treating organ failure that has become established. Adequate resuscitation to prevent continued tissue hypoxia may avoid the tissue damage that can stimulate an inflammatory response with continued release of mediators into the systemic circulation that can cause remote tissue injury and lead to MOF. The gut appears to be especially important as damage of the gut not only leads to a stimulus to inflammation from the injured cells, but also from the loss of the barrier function of the gut allowing lumenal bacteria and their toxins access to the circulation. Intestinal tonometry allows detection of dysfunction of the gut from ischemia and therefore may be important in detecting one of the major proposed etiologies of MOF. However, further evidence of its value in predicting the development of sepsis and organ failure in critically ill patients is required.

Intestinal tonometry has been shown to correlate with mortality in critically ill patients.[53,66,73,76] Two of these studies have shown that patients with gastric mucosal acidosis at admission as well as at 12 hours have a higher mortality.[66,76] Tonometry has also been correlated with presence of sepsis and MOF at ICU admission.[62,73,76] However, correlation between low pHi and

organ failure at admission does not support a causal relationship between mucosal acidosis and organ failure. For tonometry to be clinically useful, gastric mucosal acidosis has to be predictive for the development of sepsis and organ failure. Also, if interventions are to be performed on the basis of pHi to prevent sepsis, organ failure and death, then one needs to know the length of time mucosal acidosis can be tolerated. Immediate determination of pHi is not possible and therefore the length of time mucosal acidosis can be tolerated needs to be long enough to allow for measurement of pHi between interventions to try to correct it. These are major areas that have not been established in the literature and therefore need to be clarified before widespread use of tonometry can be promoted. The purpose of this study is to assess the relationship between the presence and duration of gastric mucosal acidosis and the development of sepsis and organ failure.

METHODS

I Study Hypothesis

Hypothesis

This study was designed as a prospective observational trial to test the null hypothesis:

H_0: The presence and duration of gastric mucosal acidosis has no correlation with the development of sepsis and multiple organ failure in the critically ill patient.

If the null hypothesis were to prove invalid, correction of gut dysoxia may become a method of preventing organ failure and death.

Primary outcome measures

Our primary outcome measures were organ failure as determined by the OSF score and sepsis as determined by the SSS.

Secondary outcome measures

Our secondary outcome measures were the length of ICU stay, hospital stay, and hospital mortality.

II Study Population

Recruitment

This study was performed at the University of Alberta Hospital in the general system ICU from December 16, 1993 to May 16, 1994.

Inclusion criteria

The inclusion criteria for this study were all patients admitted to the ICU that required endotracheal intubation, placement of an indwelling arterial line and who had a predicted ICU stay of at least 48 hours.

Exclusion criteria

Patients were excluded if they were less than 16 years of age, had a contra-indication to gastric intubation (ie. varices with coagulopathy; basal skull fracture; recent upper gastrointestinal anastomosis),

were Jehovah's Witness (to avoid blood loss associated with arterial blood gas determinations) or had an allergy to H_2 antagonists.

Population size

Approximately 40% of ICU patients have gastric mucosal acidosis on admission.[76] It was determined that to show a significant correlation between pHi and outcome with one-tailed significance of 0.05 and allowing for unequal sample sizes and with pHi having a medium effect (difference of 25%) that an overall sample size of 140 patients would be required. The general systems ICU at the University of Alberta Hospital averages over 600 patient admissions per year. It was felt that approximately half of the patients admitted to the ICU would meet the study criteria. It was therefore estimated that the study would enroll patients for approximately five to six months.

Patients admitted after elective or emergency surgery as well as all trauma patients were considered to be surgical admissions. All patients not fulfilling these criteria were considered medical admissions.

III Data Collection

The following data were collected on each patient at the time of admission (see appendices 5 & 6):

- age
- gender
- time and date of hospital admission
- time and date of ICU admission
- reason for admission
- time of insult

Upon entry into the study, all patients had placement of a gastric tonometer (TRIPS-NGS catheter, Tonometrics Inc, Worcester, MA, USA) via either the nasogastric or orogastric route. Gastric placement was confirmed by injecting 50cc of air via the sump portion of the tonometer and auscultating over the epigastrium. Tonometer saline CO_2, arterial pH, arterial base excess, heart rate, MAP, and

urine output were recorded at the time of entry into the study and then at times 2h, 4h, 6h, 12h, 24h, 36h, and 48h (see appendix 7). The mucosal pHi was then calculated for each of these times using a standardized process suggested by the manufacturers of the tonometers (see appendix 4). Arterial blood gas and saline CO_2 measurements were performed on a standard blood gas analyzer (Corning 278 Blood Gas System, CIBA/Corning Medical, Medfield, MA). All patients were treated with an H_2 antagonist (ranitidine) for at least the first 48 hours of the study to prevent false elevation of the mucosal CO_2 from interaction of duodenal bicarbonate with gastric acid. The sump portion of the tonometer was used for gastric decompression as per standard ICU practice.

All patients received standard ICU care as deemed appropriate. The physicians caring for the patients were blinded to the results of the mucosal pHi and therefore no treatment decisions were based on gastric pHi. Patients that improved and were discharged from the ICU prior to 48 hours had their tonometers and arterial catheters removed at ICU discharge and thus pHi measurements were also discontinued. All patients were followed daily until death or hospital discharge (study endpoints).

The following criteria were used for measurements taken during the first 48 hours of the study:

- gastric mucosal acidosis was defined as a pHi $\leq$ 7.35
- systemic acidosis was defined as pHa $\leq$ 7.30
- systemic alkalosis was defined as pHa $>$ 7.50
- tachycardia was defined as a heart rate $>$ 109 beats/minute
- hypotension was defined as MAP $<$ 70mm Hg
- oliguria was defined as urine output $<$ 50mL/hour.

Our primary outcomes were the development of sepsis and organ failure. These were quantitated using standardized scoring systems (see appendices 2 & 3).[16,17,120] OSF and SSS scores were calculated daily on all patients until death or hospital discharge. Patients were also followed for complications from the tonometers. An initial APACHE II score was calculated at the end of the first day in the ICU to allow for scoring of the severity of illness in individual patients as well as for evaluation of the study population as a whole (see appendix 1).[11] APACHE II scores were also calculated daily until death or discharge and the maximum APACHE II score recorded. The use of APACHE II for prediction

of outcome after the first day has not been validated but is widely used as an indicator of the severity of illness in critically ill patients during their ICU stay. The secondary outcome measurements in this study were length of ICU stay, hospital stay, and hospital mortality.

Data collection was all performed by the author on standard data collection sheets (see appendices 6 - 9). Data was then entered into a computerized database program (Microsoft Excel for Windows, version 3.0, Microsoft Co., Redmond, WA, USA) on an IBM compatible 386 computer. All data entered was verified on at least three occasions.

IV Ethics

Request for ethical review was presented to the University of Alberta Faculty of Medicine Research Ethics Board in June 1993. This committee felt that an individual patient consent form was not required as placement of a nasogastric tube and measurement of arterial blood gases are both part of standard ICU care. Also, this study was observational and no interventions were made on the basis of the study results. An information sheet for the patient and family was placed on each chart (see appendix 10). The Research Ethics Board reviewed the study protocols, found them acceptable and granted approval for the project in June 1993.

Clinical research at the University of Alberta Hospital also requires approval of the Special Services and Research Committee (SSRC). The study protocol was submitted to the SSRC in June of 1993. SSRC approval was received in December 1993.

V Statistics

All statistical analysis were performed on an IBM compatible 386 computer using a commercially available program (WinSTAT, Version 2.0, 1992, Kalmia Co. Inc.). Admission demographic variables were compared using a 2-tailed t-test for parametric variables and a χ-square test for categorical variables. The association between mucosal acidosis and the outcome variables of OSF score, SSS, duration of organ failure, ICU stay and hospital stay was evaluated using a t-test and taking a one-tailed p-value < 0.05 as significant. The relationship between the duration of acidosis and the

outcome variables of OSF score, duration of organ failure, ICU stay and hospital stay was evaluated by Pearson's correlation. A Spearman rank correlation was used to assess the relationship between the duration of gastric mucosal acidosis and the SSS (as the SSS is a noncontinuous variable). A t-test was used to assess the significance of the effect of the duration of mucosal acidosis on mortality.

Multiple regression analysis was performed in a direct and then a stepwise fashion to evaluate which physiological variables (age; gender; gastric mucosal acidosis, systemic acidosis or alkalosis, tachycardia, hypotension, or oliguria during the first 48 hours; duration of gastric mucosal acidosis; duration of systemic acidosis or alkalosis; duration of tachycardia; duration of hypotension; duration of oliguria; and initial APACHE II score) had independent prognostic significance for our outcome measures (OSF score, SSS, ICU stay, and hospital stay). Multiple logistic regression was used to evaluate the same variables with regard to hospital mortality.

RESULTS

During the study period, a total of 48 patients were entered into the study. Our overall study population was smaller than originally proposed (48 *vs.* 140) due to two factors. Because of unforseen delays in SSRC approval, our study started later than originally proposed. Patient accrual was also slower than anticipated with fewer patients qualifying than estimated originally and reluctance on the part of the ICU staff to enroll patients in spite of their prior commitment to do so. Fortunately, however, the effect difference was greater than the 25% predicted allowing us to evaluate our data with fewer patients. All patients were followed to hospital discharge or death. There were no complications attributable to tonometer placement.

The demographic characteristics of the study population are shown in table 2. There were no significant differences between the patients with mucosal acidosis and those without mucosal acidosis with regard to age, sex, APACHE II score at admission, or surgical *vs.* medical admission (APACHE II score, age, and medical *vs.* surgical admission have all been shown previously to affect outcome). We also compared the patients with gastric mucosal acidosis to those patients without gastric mucosal acidosis with respect to other physiological variables during the first 48 hours. We found that these patients did not differ in the presence or absence of systemic acidosis or alkalosis, tachycardia, or oliguria. However, those patients without gastric mucosal acidosis were more likely to experience systemic arterial hypotension.

Patients with and without mucosal acidosis during the first 48 hours of the study are compared with respect to outcome measures in table 3. This is represented graphically in figures 1 and 2. Patients with mucosal acidosis had a higher number of organ systems fail. The length of time these patients remained in organ failure also tended to be longer (11.2 $\pm$ 18.2 days *vs* 5.4 $\pm$ 6.9 days) although this did not reach statistical significance ($p = 0.074$). Patients with low pHi had higher sepsis severity scores than those patients that did not. Patients with gastric mucosal acidosis were also in the ICU for longer and tended to have longer hospital stays. These results became more significant when patients that died were excluded with longer ICU stays (14.5 $\pm$ 19.6 days *vs.* 3.9 $\pm$ 2.5 days; $p < 0.05$) and longer hospital stays (33.0 $\pm$ 28.2 days *vs.* 18.3 $\pm$ 7.0 days; $p < 0.05$) in patients with mucosal acidosis

during the first 48 hours in the ICU. The mortality rate was higher in patients with mucosal acidosis (39% *vs.* 18%) but this difference did not reach statistical significance ($p = 0.065$). Patient characteristics of all patients that died are included in table 5.

The correlations between the duration of acidosis and the outcome measures is presented in table 4. The duration of gastric mucosal acidosis strongly correlated with the organ failure and sepsis severity scores. Patients with mucosal acidosis for longer periods were more likely to have organ failure for longer and longer ICU stays, but these correlations were weak ($R^2 = 0.186$, $p > 0.05$ and $R^2 = 0.232$, $p > 0.05$, respectively). There was no significant correlation between duration of acidosis and length of hospital stay. However, when patients that died were excluded, the correlation between duration of acidosis and length of ICU and hospital stays became much stronger. Patients with a longer duration of acidosis were more likely to die in hospital than were those patients with shorter duration of mucosal acidosis or no mucosal acidosis at all (t-test, $p < 0.05$).

Multiple regression analysis revealed that the duration of acidosis, initial APACHE II score, and presence of oliguria during the first 48 hours were the only variables that were independent predictors for the OSF score (see table 6). The only independent predictors of the SSS on multiple regression were the duration of acidosis and the initial APACHE II score (see table 7). The duration of tachycardia was the only independent variable predictive for length of ICU and hospital stays (see tables 8 & 9). Logistic regression analysis showed that only the initial APACHE II score and age were independent variables predictive of mortality (see table 10). However, when the APACHE II score was excluded from the model, the duration of acidosis became an independent predictor of mortality with an odds ratio of 1.06 ($p < 0.05$).

DISCUSSION

The field of critical care has evolved over the past several decades. As advances have been made in the understanding of the pathophysiology of the various insults that can cause a patient to become critically ill, management of these patients has improved, often with improved patient outcome. However, despite these improvements, mortality and morbidity for critically ill patients remains high. Early deaths from shock have decreased but late deaths from sepsis and multiple organ failure have increased, now being the most common causes of death in most ICU populations. The treatment of established organ failure is costly and also increases length of ICU and hospital stay with further increase in cost.

It is recognized that the prevention of organ failure is more effective than treatment of organ failure that is already established. This an area of active interest in critical care and much current research is focussed in this area. As reviewed earlier, the pathophysiology of the development of sepsis and organ failure is still incompletely understood. However, most feel that it is the host response to an ongoing insult with systemic release of inflammatory mediators that leads to the manifestations of sepsis and causes the remote tissue injury that leads to organ dysfunction.

The recognition that some patients who appear to be resuscitated from shock still go on to develop serious complications and die has led to the concept of covert compensated shock. These patients have normal hemodynamic parameters such as blood pressure, heart rate and urine output but still have tissues that are ischemic. Detection of these patients remains difficult and no best method has yet been developed. Ideally, the monitoring should be noninvasive, inexpensive, easy to perform, and provide continuous and immediately available parameters on which to make a clinical decision. Interventions to correct these parameters should result in improved patient outcome.

Shoemaker and others have suggested the use of pulmonary artery catheters to determine DO_2 and VO_2. This method requires placement of a pulmonary artery catheter and resuscitation to "supranormal" levels. As such, it is invasive, expensive, time consuming and does not have well defined parameters to follow. It also has not been definitely shown to improve patient outcome.

Intestinal tonometry has been proposed to be an alternative method of detecting patients in "covert compensated shock" by Fiddian-Green and others. Tonometry has the advantages of being noninvasive, having relatively well defined parameters of "normal", allowing for detection of end-organ tissue dysfunction, and of monitoring the mesenteric circulation which is felt by many to be important in the development of MOF. It has been show to be predictive of development of complications and mortality in certain subsets of critically ill patients. However, it is relatively expensive, time consuming, and requires at least thirty minutes between measurements, and therefore, many remain skeptical of its value. Before adoption of tonometry as an alternative method of monitoring all critically ill patients, it needs to be shown to be predictive of development of complications in these patients.

We looked at the use of tonometry in critically ill patients to see if it is predictive of patient outcome. In particular, we looked at the development of sepsis and organ failure using objective scoring systems. We showed that patients with gastric mucosal acidosis at any time during the first forty eight hours of ICU care are more likely to have the manifestations of sepsis and to go on to develop organ failure. These patients also have organ failure for a longer length of time with a resultant increase in the length of ICU and hospital stay. Not only do these have a significant impact on the individual patient and their families, but this also results in a greater burden on health care resources.

The mortality rate was higher in patients with gastric mucosal acidosis than it was in patients without acidosis, but this did not reach statistical significance. Most of these patients died from complications of sepsis and multiple organ failure (see table 5). In contrast, deaths in the patients without acidosis tended to be from the specific cause that led to their ICU admission (ie. respiratory failure in patients with chronic obstructive pulmonary disease).

We have also shown that with a longer duration of the mucosal acidosis, patients have higher sepsis severity scores, develop dysfunction of more organ systems, and have higher hospital mortality. Although patients with longer duration of acidosis tended to have organ failure for longer as well as to have longer ICU and hospital stays, these correlations were weaker and did not reach statistical significance. Part of these latter findings can be explained by the fact that patients with a longer duration of acidosis tended to have a higher severity of illness, tended to die early in their hospital stay, and thus

the mean length of ICU and hospital stays for all patients with gastric mucosal acidosis was shorter than if those patients that died early were excluded.

The impact of any critical illness on a patient is often severe. Patients may die early from the initial insult or go on to a late death from complications, most commonly resulting from MOF. Those patients that survive still have significant morbidity and may suffer permanent injuries such as renal failure requiring dialysis, neurologic injury impairing function, and cardiorespiratory damage limiting future activities. The patients' families are also significantly affected with the potential loss of a loved one, the emotional and financial stress of having a family member in ICU, and in those patients that survive, the potential burden of caring for someone with a permanent disability.

The financial impact on the health care system is also significant. The cost of managing a patient in the ICU as well as in a regular hospital bed are substantial. The longer the patient is in the ICU and hospital, the greater these costs. The management of organ failure is also expensive and consumes a great deal of equipment and personnel resources. Chronic ventilation of patients with respiratory failure or dialysis of patients with renal failure can have staggering costs. With increasing pressure for cost containment, the allocation of a large amount of resources to a few patients is being increasingly scrutinized. As stated earlier, prevention of the development of MOF is much more effective than treatment once MOF is established. Not only is prevention more effective than treatment, it should be cost effective.

Intestinal tonometry has been proposed for use in monitoring critically ill patients to improve outcome. However, evidence establishing the usefulness of tonometry in predicting the development of sepsis and organ failure in the general intensive care patient has been lacking. We have shown that patients with gastric mucosal acidosis during the first 48 hours in ICU develop failure of more organs, have more severe manifestations of sepsis, have their organ failure for longer, stay in ICU longer, and tend to have a longer hospital stay and higher hospital mortality. We have also shown that the longer the duration of this mucosal acidosis, the worse is the outcome that patients are likely to have. In addition, the duration of acidosis was a strong independent predictor of the OSF and SSS scores whereas the

traditional physiological parameters were not. This study supports the suggestion that tonometry may be useful in monitoring critically ill patients.

Interventions to correct gastric mucosal acidosis in critically ill patients may improve outcome.[76] Our study lends further support for this proposal and also suggests that more rapid correction (the shorter the duration of acidosis) should result in a better outcome for patients. Preventing or decreasing the development of sepsis and organ failure not only improves the outcome for individual patients, but also may decrease the cost to the health care system.

The best method of correcting mucosal acidosis has not been determined. The only study that looked at this area was a small retrospective study that suggested that dobutamine was more effective than red blood cell transfusion.[75] Prospective studies are needed to determine what the best method or methods for normalising gastric pHi are. A prospective, randomized, controlled clinical trial could then be developed using interventions to correct pHi to determine if gastric tonometry is useful in improving patient outcome. We suggest that future studies utilize outcome measures such as organ failure and sepsis in addition to mortality as our study suggests that these outcomes are more strongly predicted by mucosal acidosis than is mortality. Even if the improvement in mortality is small, prevention of organ failure could substantially decrease the morbidity for individual patients as well as decrease hospital costs. If future studies provide this evidence, the use of tonometry as a standard method for monitoring critically ill patients could be supported.

TABLE 1: CLASSIFICATION OF SHOCK

Primary Cause	Type	Underlying mechanisms	Examples
Inadequate circulating blood volume	Hypovolemic shock	Hemorrhage; third space loss; dehydration	Hemorrhage; vomiting; diarrhea; bowel obstruction
	Traumatic shock (including burns)	External and or internal blood or plasma losses	Trauma; burns
	Septic shock	Third spacing; increased metabolic needs; maldistribution of blood flow	Sepsis
Loss of autonomic control of the vasculature	Neurogenic shock	Pooling of blood in denervated venous beds and excess perfusion of nonessential vascular beds	Spinal cord injury; regional anesthetic
Impaired cardiac function	Cardiac compressive shock	Compression of great veins, cardiac chambers or both	Pericardial tamponade; tension pneumothorax; ascites; hemoperitoneum; MAST pants; diaphragmatic rupture; mechanical ventilation
	Cardiogenic shock	Intrinsic abnormality of the heart	Arrhythmias; myocardial ischemia; valvular or septal defects; cardiomyopathies; coronary air embolism
	Cardiac obstructive shock	Obstruction of the pulmonary or systemic circulation	Pulmonary embolism; mechanical ventilation; pulmonary vascular disease; mechanical obstruction of aorta; systemic arteriolar constriction; polycythemia

Modified from Holcroft, J.W. and Blaisdell, F.W.: Shock: causes and management of circulatory collapse. In: Sabiston DC Jr, editor. Textbook of Surgery: the Biological Basis of Modern Surgical Practice. 14th ed.Philadelphia: Saunders, 1991:36.

TABLE 2: PATIENT DEMOGRAPHICS

	All Patients	Mucosal Acidosis (pHi ≤ 7.35)*	Normal (pHi > 7.35)	Two-tailed p-value†
Age‡	54.1 (16.8)	52.3 (18.0)	56.3 (15.4)	0.42
Males§	31 (65%)	16 (62%)	15 (68%)	0.64
Females§	17 (35%)	10 (38%)	7 (32%)	0.64
APACHE II‖	19.6 (7.5)	20.5 (8.5)	18.6 (6.2)	0.38
Surgical¶ patients§	23 (48%)	13 (50%)	10 (45%)	0.76
Medical** patients§	25 (52%)	13 (50%)	12 (55%)	0.76
Time from insult to tonometer insertion††	14.9 (19.6)	12.9 (10.6)	17.2 (26.7)	0.48

*at any point during the first 48 hours

†t-test and χ-square test where appropriate

‡in years; mean (standard deviation)

§number of patients (per cent)

‖initial score; mean (standard deviation)

¶includes all patients admitted after elective or emergency surgery, trauma patients, and patients whose primary reason for hospital admission had been for surgery or trauma

**includes all patients not qualifying as surgical patients

††in hours; mean (standard deviation)

TABLE 3: OUTCOME MEASURES FOR MUCOSAL ACIDOSIS

	All Patients	Mucosal Acidosis (pHi ≤ 7.35)*	Normal (pHi >7.35)	one-tailed p-value†
OSF Score‡	2.0 (1.1)	2.4 (1.2)	1.5 (0.7)	0.001
SSS‡	33.8 (17.9)	40.2 (19.9)	26.2 (11.6)	0.002
ICU days‡	8.0 (12.3)	10.7 (16.0)	4.8 (3.8)	0.04
Hospital days‡	20.2 (19.6)	22.9 (25.6)	17.1 (7.7)	0.14
Mortality§	14 (29%)	10 (39%)	4 (18%)	0.065
Days to OSF max.‡	2.6 (3.3)	2.5 (1.9)	2.8 (4.4)	0.37
Days to SSS max.‡	4.5 (8.7)	6.1 (11.3)	2.5 (2.8)	0.064

*at any point during the first 48 hours

†t-test

‡mean (standard deviation)

§number of deaths (per cent)

TABLE 4: OUTCOME MEASURES FOR DURATION OF ACIDOSIS

	correlation with duration of acidosis (all patients)	correlation with duration of acidosis (deaths excluded)
OSF score*	0.522‡	
SSS†	0.457‡	
ICU days*	0.232	0.413‡
Hospital days*	0.089	0.328‡

*Pearson correlation coefficient

†Spearman rank correlation coefficient

‡one-tailed significance < 0.05

TABLE 5: CHARACTERISTICS OF PATIENTS THAT DIED

Admitting diagnosis	Age*	Gender	Duration of acidosis†	APACHE II (initial)	OSF score	SSS	ICU days	Hospital Days	Cause of Death
Normal									
Pancytopenia; respiratory distress	83	male	0	31	2	41	3	5	respiratory failure
Septic arthritis; pancytopenia	74	male	0	27	2	48	3	3	sepsis; MOF
Pancreatitis; respiratory failure	73	female	0	21	1	36	13	16	ARDS; MOF
COPD; CHF; NIDDM	55	male	0	25	2	22	16	23	respiratory failure
Mucosal Acidosis									
Asthma; pneumonia	77	female	46	25	3	50	10	10	MOF
Aspiration; UGI bleed; ethanol overdose	33	male	36	35	5	75	3	3	MOF
Pancreatitis; asthma	81	male	3	21	2	45	4	9	MOF
COPD; CHF	73	female	8	27	1	22	2	2	respiratory failure
Respiratory distress; stroke	81	male	10	22	3	35	3	3	MOF
stroke	45	female	6	16	3	38	3	4	MOF
Pneumonia	62	male	12	22	5	75	7	7	MOF
CHF; COPD; hip fracture	71	female	16	33	3	41	8	10	Neurologic failure
Ischemic colitis; renal failure	63	female	24	19	4	43	3	5	MOF
Hepatic failure	36	female	48	24	4	75	4	14	MOF

*years

†hours

TABLE 6: MULTIPLE REGRESSION (STEPWISE) FOR DEPENDENT VARIABLE OSF SCORE

Independent Variables*	B	p-value
Duration of mucosal acidosis	0.03	0.005
APACHE II†	0.05	0.009
Oliguria	0.57	0.03

*Variables showing independent prognositic significance; age, mucosal acidosis, systemic acidosis or alkalosis, tachycardia, hypotension, duration of systemic acidosis or alkalosis, duration of tachycardia, duration of hypotension, and duration of oliguria included in stepwise regression analysis but not found to be independent predictors. Criteria: p-in = 0.05; p-out = 0.10.

†initial score

TABLE 7: MULTIPLE REGRESSION (STEPWISE) FOR DEPENDENT VARIABLE SSS

Independent Variables*	B	p-value
Duration of mucosal acidosis	0.57	0.004
APACHE II†	1.01	0.005

*Variables showing independent prognositic significance; age, mucosal acidosis, systemic acidosis or alkalosis, tachycardia, hypotension, oliguria, duration of systemic acidosis or alkalosis, duration of tachycardia, duration of hypotension, and duration of oliguria included in stepwise regression analysis but not found to be independent predictors. Criteria: p-in = 0.05; p-out = 0.10.

†initial score

TABLE 8: MULTIPLE REGRESSION (STEPWISE) FOR DEPENDENT VARIABLE ICU STAY*

Independent Variable†	B	p-value
Duration of tachycardia	0.67	0.0005

*with patients that died excluded

†Variable showing independent prognositic significance; age, mucosal acidosis, systemic acidosis or alkalosis, tachycardia, hypotension, oliguria, duration of mucosal acidosis, duration of systemic acidosis or alkalosis, duration of hypotension, duration of oliguria, and initial APACHE II score included in stepwise regression analysis but not found to be independent predictors. Criteria: p-in = 0.05; p-out = 0.10.

TABLE 9: MULTIPLE REGRESSION (STEPWISE) FOR

DEPENDENT VARIABLE HOSPITAL STAY*

Independent Variable†	B	p-value
Duration of tachycardia	0.87	0.003

*with patients that died excluded

†Variable showing independent prognositic significance; age, mucosal acidosis, systemic acidosis or alkalosis, tachycardia, hypotension, oliguria, duration of mucosal acidosis, duration of systemic acidosis or alkalosis, duration of hypotension, duration of oliguria, and initial APACHE II score included in stepwise regression analysis but not found to be independent predictors. Criteria: p-in = 0.05; p-out = 0.10.

TABLE 10: LOGISTIC REGRESSION FOR DEPENDENT VARIABLE MORTALITY

Independent Variables*	odds ratio	p-value
APACHE II†	1.15	0.02
Age	1.06	0.05

*Variables showing independent prognositic significance; mucosal acidosis, systemic acidosis or alkalosis, tachycardia, hypotension, oliguria, duration of mucosal acidosis, duration of systemic acidosis or alkalosis, duration of tachycardia, duration of hypotension, and duration of oliguria included in logistic regression analysis but not found to be independent predictors. Criteria: p-in = 0.05; p-out = 0.10.

†initial score

FIGURE 1: GASTRIC MUCOSAL ACIDOSIS AND OSF SCORE

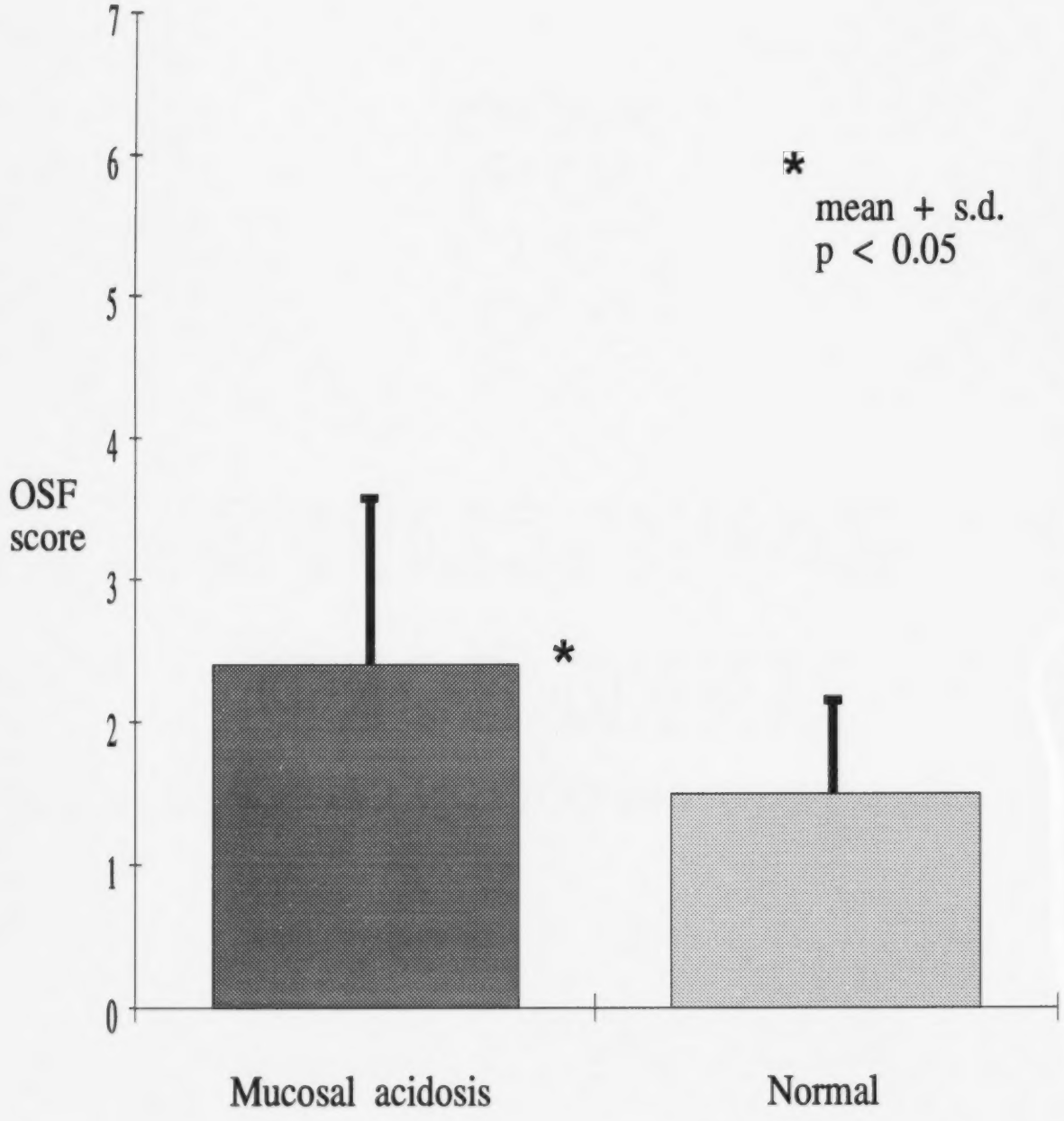
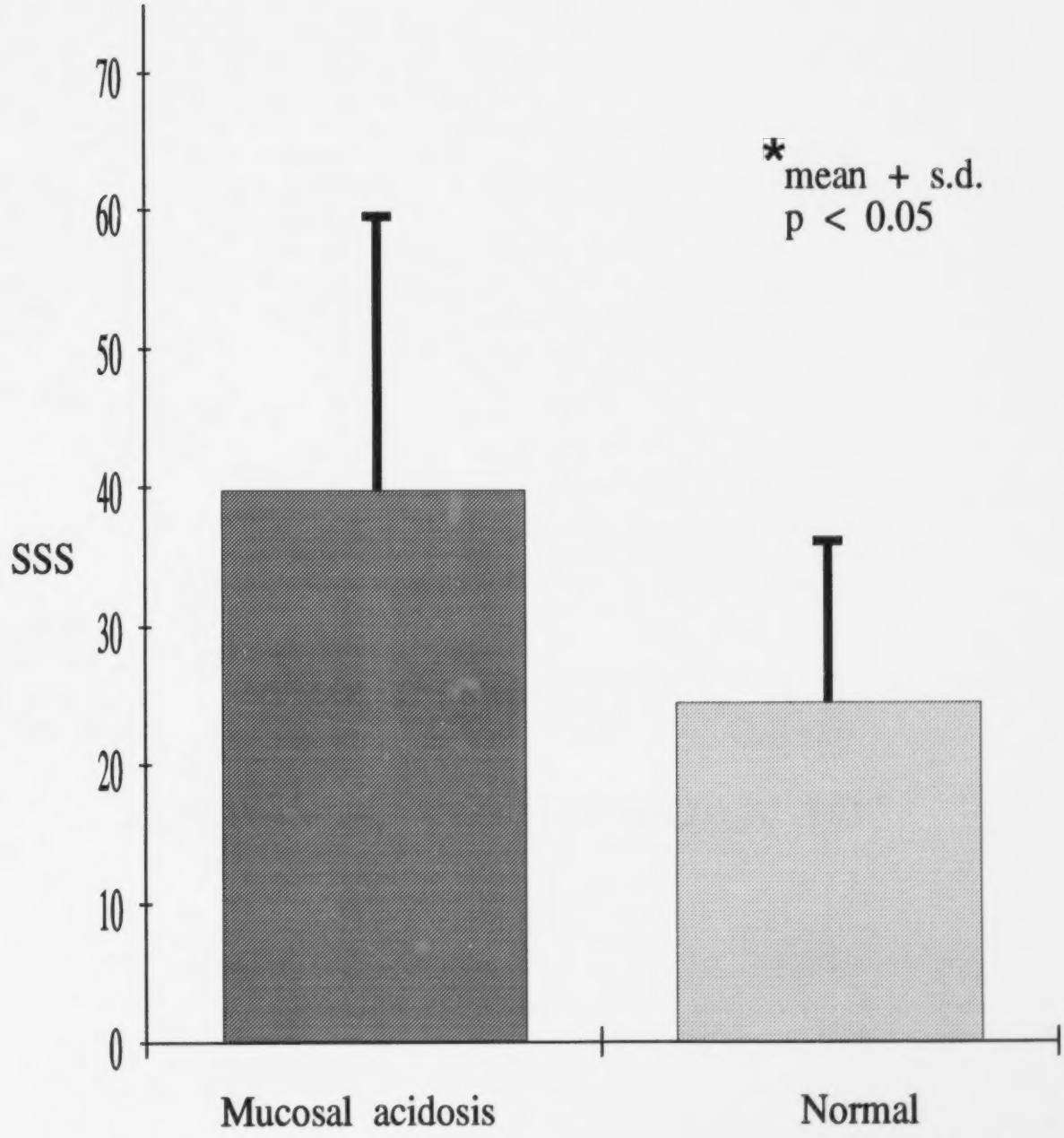


FIGURE 2: GASTRIC MUCOSAL ACIDOSIS AND SSS



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Appendix 1

APACHE II

SEVERITY OF DISEASE CLASSIFICATION SYSTEM[12]

PHYSIOLOGIC VARIABLE	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)	≥ 41°	39°-40.9°		38.5°-38.9°	36°-38.4°	34°-35.9°	32°-33.9°	30°-31.9°	≤ 29.9°
Mean Arterial Pressure - mm Hg	≥ 160	130-159	110-129		70-109		50-69		≤ 49
Heart Rate (ventricular response)	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39
Respiratory rate (non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
Oxygenation: A-aDO_2 or PaO_2 (FiO_2 ≥ 0.5)	≥ 500	350-499	200-349		< 200				
FiO_2 < 0.5 record only PaO_2					> 70	61-70		55-60	< 55
Arterial pH	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
Serum Sodium (mMol/L)	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110
Serum Potassium (mMol/L)	≥ 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
Serum Creatinine (μMol/L) (Double if acute)	> 300	169-300	125-168		53-124		< 53		
Hematocrit (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
White Blood Count ($1000/mm^3$)	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1
Glasgow Coma Score: Score = 15 - actual GCS									
[A] **Total** - Acute Physiology Score									
Serum HCO3 (venous-mMol/L) - if no ABG's	≥ 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	< 15

[B] **Age Points:**

Age (yrs)	Points
≤ 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6

[C] **Chronic Health Points:** If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:

a. for nonoperative or emergency post-operative patients - 5 points
b. for elective post-operative patients - 2 points

Appendix 1 (continued)

APACHE II

Definitions (for chronic health points):

Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria:

Liver: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

Cardiovascular: New York Heart Association Class IV.

Respiratory: Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction, ie., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mm Hg), or respirator dependency.

Renal: Receiving chronic dialysis.

Immuno-compromised: The patient has received therapy that suppresse resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g. leukemia, lymphoma, AIDS.

APACHE II Score

sum of [A] + [B] + [C]:

[A] APS Points _____
[B] Age Points _____
[C] Chronic Health Points_____
Total APACHE II Score _____

Appendix 2

Organ System Failure Score

Definitions of Organ System Failures. Organ system failure is present when any one of the following criteria are met during a 24 hour period for any given organ system. Modified from Knaus.[16]

Respiratory Failure

A. Respiratory rate <6 breaths/min or >48 breaths/min
B. $PaCO_2$ >49mm Hg
C. $AaDO_2$ >349mm Hg
where $AaDO_2 = [(713)(FiO_2) - (PaCO_2/0.8)] - PaO_2$
D. Dependence on CPAP or mechanical ventilation for >24h

Cardiovascular Failure

A. Heart rate <55 beats/min
B. Mean arterial pressure <50mm Hg (or systolic pressure $<$ 60mm Hg)
C. Occurrence of ventricular tachycardia or ventricular fibrillation
D. Serum pH <7.25 with $PaCO_2$ <50mm Hg

Renal Failure*

A. Urine output <480mL/24hours or <160mL/8hours
B. Serum urea $>36\mu$mol/L
C. Serum creatinine $>310\mu$mol/L

*excluding patients on chronic dialysis prior to hospital admission

Hematologic Failure

A. WBC $<1000/mm^3$
B. Platelets $<21{,}000/mm^3$
C. Hematocrit $<$ 21%

Neurological Failure

A. Glasgow Coma Scale $<7/15$ in the absence of sedation

Hepatic Failure

A. Serum bilirubin $>103\mu$mol/L **and** PT INR >2.0

Gastrointestinal Failure

A. Ileus (nasogastric loss >1500cc/24h)
B. Gastrointestinal bleeding requiring transfusion

Appendix 3

Septic Severity Score

	+1	+2	+3	+4	+5
Lung	O_2 by mask	Intubated, no PEEP	PEEP 0-10cm H_2O	PEEP > 10cm H_2O, PaO_2 > 50mm Hg	PEEP > 10cm H_2O, PaO_2 < 50mm Hg
Kidney	Cr 130-220μmol/L	Cr 221-310μmol/L	Cr > 310μmol/L u/o > 50mL/h	Cr > 310μmol/L u/o 20-50mL/h	Cr > 310μmol/L u/o < 20mL/h or < 500ml/24h
Cardiovascular	MAP 75-70mm Hg	MAP < 70mm Hg	Vasopressors < 6μg/kg/min	Vasopressors > 5μg/kg/min	MAP < 50mm Hg despite vasopressors
Coagulation	Ecchymoses	aPTT 45-65s, platelets normal	Platelets 100 - 20 $X10^9$, aPTT > 65s	Platelets < $20X10^9$	Increased FSP, bleeding
Liver	AST, ALT, or LDH increased (bilirubin normal)	Bilirubin 25-44μmol/L	Bilirubin 45-74μmol/L	Bilirubin 75-134μmol/L	Bilirubin > 135μmol/L, precoma
Gastro-intestinal tract	Mild ileus (nasogastric losses 500-999cc/24h)	Moderate ileus (nasogastric losses 1000-1999cc/24h)	Severe ileus (nasogastric losses > 2000cc/24h)	Bleeding erosive gastritis	Mesenteric venous thrombosis
Neurologic	Obtunded GCS 9-10/10 or 13-14/15	Disoriented GCS 7-8/10 or 10-12/15	Irrational GCS 5-6/10 or 6-9/15	Hypoactive GCS 3-4/10 or 4-5/15	Coma GCS 2/10 or 3/15

Modified from Stevens[17] and Skau[120]. The score is calculated by summing the square of the three highest rating points; PEEP, positive end-expiratory pressure; Cr, serum creatinine; u/o, urine output; MAP, mean arterial pressure; aPTT, activated partial thromboplastin time; FSP, fibrinogen split products; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; GCS, Glasgow coma scale (out of 10 when patient intubated).

Appendix 4

Calculation of Gastric Mucosal pH (pHi)

- after placement of the tonometer was confirmed, 2.5mL of saline were placed in the gas permeable silicone balloon of the tonometer to allow for equilibration of CO_2 between the gastric mucosa and the saline
- at the time of each measurement, the first 0.5mL of saline was removed and discarded, the remaining 2.0mL of saline was then removed and sent for measurement of CO_2 content, and an arterial blood gas was sent for simultaneous determination of arterial bicarbonate
- 2.5mL of fresh saline was replaced in the tonometer and left in place until the next measurement was required
- the mucosal pHi was then calculated from the tonometer saline CO_2 content and the arterial bicarbonate using a slide calculator (TRIPS-NGS Catheter pHi Slide Calculator, Tonometrics Inc, Worcester, MA, USA) that corrects for the time of equilibration.

Appendix 5

Time of Insult

1. Trauma - time of accident.

2. Elective surgery - time of incision.

3. Sepsis - first recorded evidence of infection (from Bone[89]):
   - tachypnea (respiratory rate > 20breaths/min; if mechanically ventilated, minute ventilation > 10L/min)
   - tachycardia (heart rate > 90beats/min)
   - hyperthermia or hypothermia (core or rectal temperature > 38^{O}C or < 35.5^{O}C)

4. Other (ie. pancreatitis, exacerbation of COPD, overdose, etc.)
   - difficult to identify time well
   - "best guess"
   - urine output < 0.5cc/h
   - SBP < 100mm Hg
   - serum lactate > 2.0mmol/L

Appendix 6

Data Collection Sheet 1

Demographics

Name	_____
Hospital ID #	_____
Gender	_____
Age	_____
Hospital admission (date)	_____
ICU admission (date)	_____
ICU admission (time)	_____
Time of onset of insult	_____
Time from insult to ICU	_____
Diagnosis/reason for admission	_____

Admission Vital Signs

Systolic BP	_____	mm Hg	Ventilation mode	_____	
Diastolic BP	_____	mm Hg	Rate	_____	/min
MAP	_____	mm Hg	FIO_2	_____	%
Heart rate	_____	/min	PEEP	_____	cm H_2O
Temperature	_____	C	GCS	_____	

Admission Lab Data

Hemoglobin	_____	g/dL	Sodium	_____	mmol/L
Hematocrit	_____	mL/dL	Potassium	_____	mmol/L
WBC	_____	10^9/L	Chloride	_____	mmol/L
Platelets	_____	10^9/L	Bicarbonate	_____	mmol/L
PT INR	_____		Urea	_____	mmol/L
PTT	_____	sec	Creatinine	_____	μmol/L
Lactate	_____	mmol/L	PaO_2	_____	mm Hg
Bilirubin	_____	μmol/L	$PaCO_2$	_____	mm Hg
Protein	_____	g/L	O_2 saturation	_____	%
Albumin	_____	g/L	Hydrogen	_____	mmol/L
Glucose	_____	mmol/L	Base excess	_____	

Appendix 7

Data Collection Sheet 2 (tonometry and physiologic variables)

	Entry	2h	4h	6h	12h	24h	36h	48h
Gastric Tonometer								
PaO2								
PaCO2								
Arterial [H+]								
SaO2								
Base excess								
Arterial pH								
Arterial [HCO3-]								
PiCO2								
Gastric mucosa pH								
Systemic Readings								
Heart Rate								
Mean Arterial Pressure								
Urinary Output								
lactate								
Swan Ganz (if done)								
CVP								
PCWP								
Cardiac Output								
Cardiac Index								
SVRI								
PVRI								
Mixed Venous								
Oxygen								
Carbon Dioxide								
Hydrogen								
Oxygen Saturation								
Base Excess								

Appendix 8

Data Collection Sheet 3 (OSF & APACHE II scores)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Respiratory										
Ventilated										
Resp. rate <6 or >48										
FiO2										
PaO2										
PaCO2 >49										
AaDO2 >349 [(713)(FiO2)-(PaCO2/0.8)] - PaO2										
Cardiovascular										
Pulse <55										
MAP <50mm Hg										
V.tach/V.fib										
pH <7.25 (PaCO2<50)										
Temperature										
Renal										
Urine output <480mL/24h or <160mL/8h										
Urea >35umol/L										
Creatinine >309umol/L										
Sodium										
Potassium										
Hematological										
WBC <1000										
Platelets <21										
Hematocrit <21%										
Neurological										
Sedation										
GCS <7/15 (or <5/10)										
Hepatic										
Bilirubin >102umol/L										
PT INR >2.0										
Gastrointestinal										
Ileus (NG >1500cc/24h)										
Bleeding requiring transfusion										
# of Organs Failed										
APACHE II										

Appendix 9

Data Collection Sheet 4 (SSS)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Lung										
1 - O2 by mask										
2 - intubated, no PEEP										
3 - PEEP 0-10cm H2O										
4 - PEEP >10cm H2O, PaO2 >50mm Hg										
5- PEEP > 10cm H2O, PaO2 <50mm Hg										
Kidney										
1 - Cr 130-220umol/L										
2 - Cr 221-310umol/L										
3 - Cr >310umol/L, u/o >50mL/h										
4 - Cr >310umol/L, u/o 20-50mL/h										
5 - Cr >310umol/L, u/o <20mL/h										
Cardiovascular										
1 - MAP 75-70mm Hg										
2 - MAP <70mm Hg										
3 - Vasopressors <6ug/kg/min										
4 - Vasopressors >5ug/kg/min										
5 - MAP <50mm Hg despite vasopressors										
Coagulation										
1 - Ecchymoses										
2 - aPTT 45-65s										
3 - aPTT >65s, Platelets 100-20 X 109										
4 - Platelets <20 X 109										
5 - Increased FDP, bleeding										
Liver										
1 - AST, ALT, or LDH elevated, (bili [N])										
2 - Bili 25-44umol/L										
3 - Bili 45-74umol/L										
4 - Bili 75-134umol/L										
5 - Bili >135umol/L, precoma										

Appendix 9 (continued)

Data Collection Sheet 4 (SSS)

GI tract										
1 - NG 500-1000cc/24h										
2 - NG 1000-2000cc/24h										
3 - NG >2000cc/24h										
4 - Bleeding - erosive gastritis										
5 - Mesenteric venous thrombosis										
Neurologic										
1 - GCS 9-10/10 or 13-14/15										
2 - GCS 7-8/10 or 10-12/15										
3 - GCS 5-6/10 or 6-9/15										
4 - GCS 3-4/10 or 4-5/15										
5 - GCS 2/10 or 3/15										
Septic Severity Score (sum of square of 3 highest scores)										

Appendix 10

Family and Patient Information Sheet

Information obtained from your stay (or your family member's stay) in the Intensive Care Unit (ICU) is being used as part of a study. We are studying the development of sepsis and organ failure in critically ill patients (the most common causes of death in ICU's). This involves using a special type of nasogastric tube to take measurements indicating stomach blood flow. This tube is essentially no different than those that are used routinely in the ICU apart from a small attached balloon that is used to take measurements. We will also be doing a test called an arterial blood gas that is also routinely performed in almost all ICU patients. **No pain or adverse effects will result. There is no special treatment given as part of the study.**

These special measurements will only be followed for the first 48 hours. After that we will continue to follow the hospital course until discharge. **All information will remain confidential** and no names will be used when the data are presented.

The goal of this study is to confirm that this special nasogastric tube is useful in predicting the development of sepsis and organ failure and in the future may be used to prevent their development.

If you have any further questions or concerns regarding any aspects of this study, please contact either of the following physicians who are directing the study.

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